REMARKS

Applicants have amended Claim 7, support for which is found on pages 6-7 of the specification. Applicants have canceled Claims 8 and 10. Claims 7 and 18-20 remain pending in this application.

§112, paragraph 1, Rejection

Examiner rejected claims 7, 8, 10, 18-20 in view of the first paragraph of 35 USC §112. Applicants traverse this rejection because *in vitro* phase II activity of *Echinacea purpurea* fractions are predictive if *in vivo* phase II activity. In support of its position, Applicants submit in Exhibit A a Declaration under 37 C.F.R. §1.132.

§112, paragraph 2, Rejection

Examiner rejected claims 7, 8, 10, 18-20 in view of the second paragraph of 35 U.S.C. §112. Applicants have amended Claim 1 to recite who the composition is being administered to. As such, paragraph two of §112 is believed to be satisfied.

§102(e) Rejection

Examiner rejected Claims 7, 8, 10, 18-20 under 35 U.S.C. §102(e) as being anticipated by Mitscher et al. or Raskin et al. Applicants respectfully traverse this rejection. Mitscher's earliest priority date is May 9, 2000. Applicants had possession of their invention prior to May 9, 2000 and submit in Exhibit B a Declaration under 37 C.F.R. §1.131 establishing a prior date of conception and reduction to practice. Accordingly, Mitscher is not proper §102(e) prior art.

Furthermore, Applicants submit that Raskin does not disclose all the elements of amended Claim 7. Specifically, Raskin does not disclose chloroform root fractions or acidic chloroform aerial fractions of *Echinacea purpurea*. Rather, Raskin discloses chloroform as one solvent to remove cuticular material from plant leaves (Raskin para 15). Nowhere in Raskin is there mention of adjusting the pH of the cuticular material removed by the chloroform or using chloroform on root extracts. As such, Applicants request removal of this rejection.

§103(e) Rejection over Raskin et al. or Mitscher et al.

Examiner rejected Claims 7, 8, 10, and 18-20 under 35 U.S.C. §103(a) over Mitscher et al or Raskin et al. Applicants respectfully traverse this rejection. As

explained above, because Mitscher is not proper §102(e) prior art, it cannot be used as a reference under 103(a).

With respect to Raskin, Applicants respectfully submit that Examiner has not established a proper *prima facie* case of obviousness because there is no incentive to modify Raskin and no reasonable expectation of success that the modified Raskin extract would result in the claimed method - inducing phase II enzymes with chloroform soluble *Echinacea purpurea* fractions. MPEP §2142 states that to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. MPEP §2142. Raskin does not teach or suggest that chloroform root fractions or acidic chloroform aerial fractions of *Echinacea purpurea* should be administered to subjects to induce phase II activity. Rather, Raskin teaches that chloroform can be used to remove the cuticular material on plant leaves to obtain compounds such as lipids, wax, cutin, and protein therein (Raskin para. 15). Cuticular material is not even found on *Echinacea* roots so one of ordinary skill in the art would not use the teachings of Raskin to obtain phase II induction compounds from roots. Further, there is no mention or suggestion of adjusting the pH of Raskin's cuticular leaf extract.

Even if Raskin provided incentive to use chloroform fractions of root material or acidic chloroform fractions of aerial material, using chloroform soluble extracts of *Echinacea purpurea* is not taught or suggested. One of Raskin's objectives is to identify plants having therapeutic activity such as anti-microbial and anti-cancer activity (Raskin para. 16). Raskin states that inhibition of the growth of the suspension contacted with the microorganism is indicative of an agent in the suspension having therapeutic activity (Raskin, para. 70). Raskin then tested several plant materials for their activity to inhibit microorganisms and *Echinacea purpurea* for its anti-microbial activity. Specifically,

Raskin lists *Echinacea purpurea* in a single instance - as one of several plant extracts that have no detectable anti-microbial activity (Raskin, para. 169 and page 29). This suggests that *Echinacea purpurea* is not an efficacious anti-microbial material for accomplishing Raskin's objectives. As such, one of ordinary skill in the art would not consider using Raskin's *Echinacea purpurea* material to successfully obtain an anti-microbial compound let alone phase II induction. There is no reasonable expectation of succession modifying Raskin's extract to obtain the claimed invention. Therefore, Applicants respectfully request removal of this rejection.

§103 Rejection over Intelisano or Braswell in view of Facino and over Facino

Examiner also rejected claims 7, 8, 10 and 18-20 under 35 U.S.C. §103(a) over Intelisano or Braswell in view of Facino and over Facino. Specifically, Examiner maintained that the foregoing references as a whole teach a method of inducing phase II enzymes in subjects comprising administering a chloroform soluble *Echinacea purpura* extract. These references were previously used on obviousness grounds in the Final Office Action of April 18, 2003. Applicants appealed that Action and filed an Appeal Brief on September 18, 2003 asserting that these references alone or in combination make Applicants' invention obvious. Before the Appeal was decided, Examiner re-opened prosecution by issuing a §112 rejection. Applicants, again, respectfully traverse the §103 rejections as conceivably applied to the amended claims.

Braswell states that "certain *Echinacea* extracts have shown direct anti-cancer activity *in vivo*" (column 2, lines 61-64). Facino discloses a method of purifying E*chinacea angustifolia* to obtain a choloroform fraction that has anti-hyaluronidase activity at a certain concentration and acidity (p.1450-1452). Intellisano discloses a food supplement that contains *Echinacea* for an antioxidant and suggests that *Echinacea angustifolia* and *Echinacea purpurea* are interchangeable.

A. A *Prima Facie* Case Of Obviousness Has Not Been Properly Established.

Applicants respectfully submit that Examiner has not established a proper *prima facie* case of obviousness because Braswell or Intellisano is not properly combinable with Facino as there is no reasonable expectation of success in modifying Facino's or substituting Facino's *Echinacea angustifolia* for Braswell or Intellisanos' *Echinacea.* Further, this combination does not teach or suggest all the claim limitations, namely,

inducing phase II enzymes with chloroform-soluble *Echinace purpurea* fractions. The concentration of actives responsible for *Echinacea*'s beneficial effects vary from species to species. It is known by one of ordinary skill in the art that a chloroform fraction from any *Echinacea* species, at any acidity, and at any concentration would not necessarily achieve the same levels of phase II activity and anti-hyaluronidase activity as suggested by Examiner. In fact, the data in support of anti-hyaluronidase activity in Facino and the data in support of Applicant's phase II activity demonstrate that different results can be achieved with different materials and concentrations. See arguments in Section B herein. Because several variables can alter the ability of *Echinacea* to induce phase II enzymes, there is no reasonable expectation of success. The modification or combination of the prior art make it, at best, obvious to try the claimed method but do not make the claimed method for inducing phase II with chloroform soluble fractions of *Echinacea purpurea* obvious without hindsight reconstruction. Obvious to try is not a sufficient basis for a prima facie case.

Additionally, a *prima facie* case has not been properly established because all the claimed limitations are not met. See MPEP §2143.03. None of the cited references teach or suggest the specific method of inducing phase II by administering chloroform-soluble *Echinacea purpurea* fractions selected from either chloroform root fractions or acidic chloroform aerial fractions. Because none of the cited references teach or suggest the claimed method for inducing phase II enzymes, the rejection under §103(a) is improper and this rejection should be withdrawn.

B. Applicant's Method Provides Surprising Results.

Even if the references are properly combined, Applicants believe that the claimed invention is not obvious over the cited art because Applicants' invention provides surprising results as outlined throughout the present specification. MPEP §2144.09 states that, "A prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties." Applicants have found that the chloroform-soluble chloroform portion of *Echinacea purpurea* performs surprisingly better than other *Echinacea purpurea* fractions in inducing phase II activity. The phase II inducing activity of the chloroform-soluble fraction is greater than one would expect given the prior art teachings. A greater

than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...of the claims at issue. See MPEP §716.02(a) and In re Corkill, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). In the present case, the chloroform fraction (at a neutral ph) of Facino's *angustifolia* shows inferior hyaluronidase inhibition when compared with the ethylacetate fraction (page 1451, paragraph 4 and page 1452, Fig. 1). As such, if one assumed that *purpurea* and *angustifolia* were interchangeable and affected hyaluronidase inhibition and phase II enzyme induction equally (as suggested by Examiner), one would expect that the chloroform root fraction of Applicants' *Echinacea purpurea* would be inferior to the ethylacetate fraction. In contrast, Applicants' chloroform root fraction provides surprisingly superior phase II induction results than the ethylacetate fraction as shown in Fig. 2 of the present application. Moreover, Applicants' claimed method provides surprising results because the level of enzyme activity in the chloroform root fraction was 35% higher than the root methanol fraction; the acidic chloroform aerial fraction was 87% higher than the more polar methanol fraction (see p.5, lines 15-20). At 0.09mg/ml of *Echinacea purpurea* extract, the chloroform root fraction had 1.86 times the quinone reductase activity of the untreated control (page 9, lines 26-28). Therefore, Applicants believe that the claimed method of inducing phase II enzyme by administering a chloroform root fraction or an acidic chloroform aerial fraction of *Echinacea purpurea* is not obvious and is patentable over the prior art.

Conclusion

Applicants have made an earnest effort to place their application in proper form and to distinguish their invention as presently claimed from the cited prior art. Therefore, Applicants respectfully request entry of the amendments and allowance of the pending claims. It is also respectfully requested that the Examiner expeditiously notify the undersigned attorney as to the disposition of the arguments presented herein in accordance with MPEP §714.13.

Respectfully submitted,

By: Brovelli et al.

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